s 244

Kathy B. Burck
Edison T. Liu
James W. Larrick

Oncogenes

An Introduction to the Concept of Cancer Genes

With a Foreword by Joshua Lederberg

With 93 Figures, 8 in Full Color

1988

Springer-Verlag
New York Berlin Heidelberg
London Paris Tokyo

Foreword

"Cancer viruses" have played a paradoxical role in the history of cancer research. Discovered in 1911 by Peyton Rous (1) at the Rockefeller Institute, they were largely ignored for several decades. Witness his eventual recognition for a Nobel Prize, but not until 1966 – setting an all time record for latency, and testimony to one more advantage of longevity.

In the 1950s, another Rockefeller Nobelist, Wendell Stanley, spearheaded a campaign to focus attention on viruses as etiological agents in cancer, his platform having been the chemical characterization of the tobacco mosaic virus as a pure protein – correction, ribonucleoprotein – in 1935 (2). This doctrine was a centerpiece of the U.S. National Cancer Crusade of 1971: if human cancers were caused by viruses, the central task was to isolate them and prepare vaccines for immunization. At that point, many observers felt that perhaps too much attention was being devoted to cancer viruses. It was problematic whether viruses played an etiological role in more than a handful of human cancers.

Nevertheless, some cancers were indubitably rooted in virus infection. What overarching concept could unify these observations with cancer induced by a range of environmental influences, ranging from hormones to poison gas to radiation?

The keys to this puzzle emerged out of a galaxy of microbial and cell biological studies that initially had no relationship to viruses. Alexander Haddow (1937) (3) and others formulated cancer as a somatic mutation, a change in the chromosomes (now we say DNA) of a somatic cell. Some contributory evidence that emerged was the overlap in biological activity of radiation and some carcinogenic chemicals: many of them could both cause tumors and induce mutations. And the cancer transformation was a hereditarily stable alteration of a cell clone. The theory could not, however, give a simple account of hormonal induction of cancers; not until the metabolic studies of the Millers (4) could we understand other discrepancies, like the carcinogenic activity of azo dyes and of polycyclic hydrocarbons. Nor did the theory explain viral cancers. In 1946, Lederberg (5) suggested that neoplasia resembled growth-restoring mutations in nutritionally regulated microbes, and speculated that viruses might mimic mutations by the import of extraneous genetic information. But there was no way to test the theory; absent were methods for the study of the genetics of somatic cells.

The first major breakthrough came from the study of pneumococcal transformation, and the epochal finding of Avery, MacLeod, and McCarty (1944) (6) that the agent of genetic transfer was DNA. The conflagration inspired by that work embraces almost all of contemporary biology. However, Avery did not have the luck to survive another 55 years, which would surely have won him recognition in Stockholm. It immediately impelled a rush of work on the genetics of bacteria, organisms that—like somatic cells—had been thought beyond the reach of genetic analysis. The discovery of recombination in *Escherichia coli* (1946) (7) was followed by that of virus-mediated transduction in *Salmonella* (1952) (8). This gave firm substantiation to the concept that genetic information could be transmitted from cell to cell by a virus. In the example of lysogenic conversion, information critical to the ecological functioning of the host was an integral part of the viral genome (9).

By the mid-1950s it was possible to declare a manifesto for somatic cell genetics (10). That the correct elucidation of the human karyotype, $2n = 46$, took until 1956 (11) reminds us how primitive was our approach to somatic cells until the current generation. The advent of methods of somatic cell fusion opened the door to systematic mapping of somatic genomes in the 1960s (12), soon to be followed by the molecular genetic analyses of the current era.

The latter are the meat of this book. Oncogenes have become a central theme of contemporary molecular biology. Oncogene research addresses, of course, one of the most grievous of life's burdens, the disease of cancer. It is tautological that the understanding of cancer is inseparable from that of normal development. Rarely, if ever, is the oncogene an adventitious trick wholly invented by the predatory virus. Instead it is a subtle variant on an indigenous system of genic regulation. Cancer viruses have receded as a primary exogenous cause of human cancers. But we are in some measure lucky to have found them, for they have given us the most substantial clues to the occurrence of oncogenes within the human genome—the bits of DNA whose alteration by any means engenders cellular dysregulation and neoplasia.

No one interested in cancer, in viruses, in the cell biology of normal development—whom does that leave out?—can afford to be bereft of the overview of contemporary knowledge that is lucidly and comprehensively surveyed in this book.

Joshua Lederberg
The Rockefeller University

References

1. Rous P. A sarcoma of the fowl transmissible by an agent separable from the tumor cell. J Exp Med 13:397–411, 1911.
2. Stanley WM. Isolation of a crystalline protein possessing the properties of tobacco mosaic virus. Science 81:644–645, 1935.

3. Haddow A. Secondary colony formation in bacteria and an analogy with tumour production in higher forms. Acta Int Union Against Cancer 2:376–401, 1937.
4. Miller EC, Miller JA. Biochemistry of carcinogenesis. Annu Rev Biochem 28:291–320, 1955.
5. Lederberg J. A nutritional concept of cancer. Science 104:428, 1946. Where I quote my own work and thought it is for proximate familiarity, not any claim of uniqueness or priority. I appreciate the authors' asking me to contribute some archeological perspectives: une "recherche du temps perdu."
6. Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation on pneumococcal types. J Exp Med 79:137–158, 1944.
7. See: Lederberg J. Genetic recombination in bacteria: a discovery account. Annu Rev Genet 21:23–46, 1987.
8. Zinder ND, Lederberg J. Genetic exchange in *Salmonella*. J Bacteriol 64:679–699, 1952.
9. Freeman VJ. Studies on the virulence of bacteriophage-infected strains of *Corynebacterium diphtheriae*. J Bacteriol 61:675–688, 1951.
10. Lederberg J. Prospects for the genetics and somatic and tumor cells. Ann NY Acad Sci 63:662–665, 1956.
11. Tjio JH, Levan A. The chromosome numbers of man. Hereditas 42:1–6, 1956.
12. See, i.e., Ruddle FH, Creagan RP. Parasexual approaches to the genetics of man. Annu Rev Genet 9:407–493, 1975.